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54	TITLE OF INVENTION

AGENT FOR TRANSDERMAL ADMINISTRATION CONTAINING ESTERS OF 13-ETHYL-17ß-HYDROXY-11-METHYLENE-18,19-DINOR-17α-PREGN-4-EN-20-YN-3-ONE

57	ABSTRACT (NOT MORE THAN 150 WORDS)

NUMBER OF SHEETS 32

The sheet(s) containing the abstract is/are attached.

If no classification is furnished, Form P.9 should accompany this form.
The figure of the drawing to which the abstract refers is attached.

Abstract:

An agent for transdermal administration is described that is characterised in that it contains esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one having from 1 to 20 carbon atoms in the ester radical, optionally in combination with one or two oestrogen(s).

FIGURE FOR PUBLICATION

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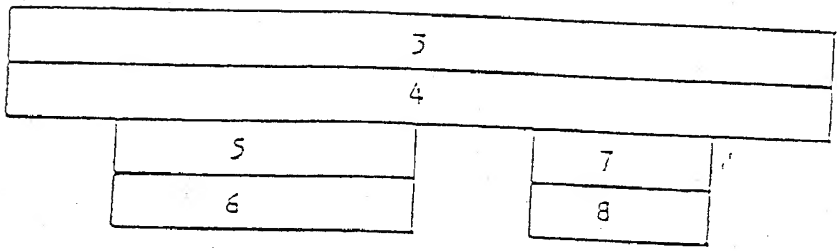
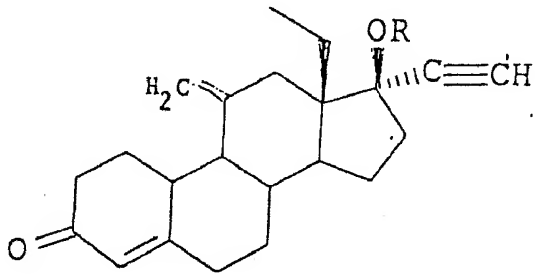


Fig. 2

Agent for transdermal administration containing esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one

The invention relates to an agent for transdermal administration, which is characterised in that it contains esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one having from 1 to 20 carbon atoms in the ester radical, optionally in combination with one or more oestrogen(s).

Those esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one are characterised by the general formula



wherein R is an acyl radical having from 1 to 20 carbon atoms.

The invention relates preferably to agents for transdermal administration that contain esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one having from 2 to 12 carbon atoms in the acyl radical and especially to agents that contain alkanoyl esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one having from 2 to 8 carbon atoms in the alkanoyl radical. As suitable, hitherto-unknown esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one special prominence is given to the acetate, the butyrate and, especially, the hexanoate thereof, to which the present invention

also relates and the preparation of which will be described hereinafter.

13-Ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one itself is known to be a substance having an extraordinarily high gestagenic activity which is used in the form of its pro-drug, 13-ethyl-11-methylene-18,19-dinor-17α-pregn-4-en-17ß-ol (J. of Steroid Biochem., 14, 1981, 175 ff. and Europ. J. of Clin. Pharmacol., 15, 1979, 349 ff.), in combination with oestrogenically active compounds for the preparation of agents having a contraceptive action that are to be administered orally (Marvelon®).

It has now been found that, surprisingly, the esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one, optionally in combination with one or more oestrogens, can often be used better for the preparation of an agent for transdermal administration of the active ingredients than can combination preparations that contain 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one itself.

By esterifying the hydroxyl group in the 17ß-position of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one the physico-chemical properties of that substance are altered specifically and bioreversibly in the sense of a pro-drug formation.

If one compares the skin penetration of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one with that of its esters, the latter are generally distinguished by markedly higher transdermal flows. That is especially true when the esters are processed into matrix transdermal systems, such as, for example, those of the acrylate type (as are described hereinafter in

Example 2).

The extraordinarily high transdermal flows can be explained, in particular, by the surprisingly favourable solubilities that the said esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one have been found to have in the customary skin-adhesives and mixtures thereof with co-solvents and penetration-enhancers. By virtue of that property, it is now possible for the first time to prepare highly charged and stable matrix transdermal systems with molecularly disperse pro-drugs. Even active ingredient charges that, on a molecular basis, are 15 times higher than the comparable charges that can be achieved with 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one itself result in stable systems. This is a crucial advantage over systems containing 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one that are prior-known from WO 94/04157, since the concentration fall between transdermal systems and skin is decisively responsible for the level of the transdermal flows that are achievable.

It is therefore possible by means of the agent according to the invention to achieve high, uniform flows of esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one using comparatively small transdermal systems.

It has already been mentioned that, in addition to containing the gestagen, the agent according to the invention may also contain one or more oestrogens. Suitable oestrogens are, for example, oestradiol, oestriol, ethinyloestradiol, mestranol, 14α,17α-ethanoestra-1,3,5(10)-triene-3,17ß-diol (WO 88/01275), 14α,17α-ethanoestra-1,3,5(10)-triene-3,16α,17ß-triol

(WO 91/08219) and esters thereof (EP-A 163 596), such as oestradiol dipropionate, oestradiol dihexanoate and oestradiol didecanoate. These combination preparations according to the invention contain, in addition to 1 or 2 gestodene esters, preferably from 1 to 3, especially 1 or 2, oestrogen(s).

For the manufacture of pharmaceutical preparations the active ingredient or active ingredient mixture may be dissolved or suspended in suitable volatile solvents and/or penetration-enhancing agents. The resulting solutions or suspensions may be combined with customary adjuvants, such as matrix formers and bactericides, and, where appropriate after sterilisation, introduced into customary dosing vessels. On the other hand, it is also possible, however, to process those solutions or suspensions further, with the incorporation of emulsifiers and water, to form lotions or ointments. It is also possible to produce sprays - optionally with the addition of propellant gas - which can be introduced into the customary dosing vessels.

Suitable volatile solvents are, for example, lower alcohols, ketones or lower carboxylic acid esters, such as ethanol, isopropanol, acetone or ethyl acetate, polar ethers, such as tetrahydrofuran, lower hydrocarbons, such as n-hexane, cyclohexane or benzine, or also halogenated hydrocarbons, such as dichloromethane, trichloromethane, trichlorotrifluoroethane and trichlorofluoromethane. It goes without saying that mixtures of those solvents are also suitable.

Suitable penetration-enhancing agents are, for example, monohydric or polyhydric alcohols, such as ethanol, 1,2-propanediol or benzyl alcohol, saturated and unsaturated

fatty alcohols having from 8 to 18 carbon atoms, such as lauryl alcohol or cetyl alcohol, hydrocarbons, such as mineral oil, saturated and unsaturated fatty acids having from 8 to 18 carbon atoms, such as stearic acid or oleic acid, fatty acid esters having up to 24 carbon atoms or dicarboxylic acid diesters having up to 24 carbon atoms.

Fatty acid esters that are suitable as penetration-enhancing agents are, for example, those of acetic acid, caproic acid, lauric acid, myristic acid, stearic acid, palmitic acid or oleic acid, such as, for example, the methyl esters, ethyl esters, propyl esters, isopropyl esters, butyl esters, sec.-butyl esters, isobutyl esters, tert.-butyl esters or monoglycerol esters of those acids. Especially preferred esters are those of myristic acid or oleic acid, such as the methyl esters, isopropyl esters or monoglycerol esters thereof. Suitable dicarboxylic acid diesters are, for example, diisopropyl adipate, diisobutyl adipate and diisopropyl sebacate.

Other penetration-enhancing agents are phosphatide derivatives, such as lecithin, terpenes, amides, ketones, urea and its derivatives, or ethers, such as, for example, diethylene glycol monoethyl ether or dimethyl isosorbide. It goes without saying that mixtures of those penetration-enhancing agents are also suitable for the preparation of the agent according to the invention.

The concentration in which the active ingredient or active ingredient mixture is optimally dissolved or suspended in the solvent is usually from 0.01 to 40 % by weight for the esters of 13-ethyl-17ß-hydroxy-11-methyl-ene-18,19-dinor-17α-pregn-4-en-20-yn-3-one. In the case of the oestrogens, the concentration is naturally dependent on the nature of the active ingredient used and on the desired individual dose and has to be determined

in the individual case by means of preliminary tests familiar to one skilled in the art, for example determination of the concentrations of active ingredient that can be achieved in the plasma, after dermal administration of selected systems according to the invention. In general, in this case also, active ingredient concentrations of from 0.01 to 25 % by weight oestrogen in the agent according to the invention will be sufficient. The weight ratio of the ester of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one to the oestrogen(s) in the case of the combination preparations is from 5:1 to 1:10.

The therapeutically required transdermal daily dose depends on the indication and is in the range of approximately from 30 to 120 µg of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one per day. The esters of 13-ethyl-17ß-hexanoyloxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one are dosed in equimolar amounts in order to take account of the increase in molecular weight as a result of the pro-drug formation. For example, the daily dose for 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one is approximately from 40 to 150 µg. Based on a transdermal system having a surface area of 20 cm^2, this means that transdermal flows of up to 0.3 µg of 13-ethyl-17ß-hexanoyloxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one/cm^2/hour are required. In <u>in vitro</u> studies with suitable formulations it has been possible to show that those flows are clearly exceeded.

A very uniform administration with a set dosage of the active ingredient or active ingredient mixture can be achieved when the active ingredient or the mixture is embedded in a transdermal therapeutic system (TTS). Suitable transdermal therapeutic systems are those which

are customarily employed for percutaneous administration of active ingredients (Yie W. Chien: "Transdermal Controlled Systemic Medications", Marcel Dekker Inc., New York and Basle 1987, Dr. Richard Baker: "Analysis of Transdermal Drug Delivery Patents 1934 to 1984" and "Analysis of Recent Transdermal Delivery Patents, 1984-1986 and Enhancers" Membrane Technology & Research 1030 Hamilton Court Menlo Park CA 94025 (415) 328-2228).

It is therefore possible to use, for example, a transdermal therapeutic system that consists of

a) an impermeable cover layer,
from one to three matrix layer(s) which adhere(s) to the cover layer, which contain(s) the ester(s) of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one, optionally the oestrogen(s) and, if desired, penetration-enhancing agents and is(are) permeable to those components, and which is(are) self-adhesive or covered or surrounded by a skin-adhesive that, if desired, contains penetration-enhancing agents,
and a removable protective layer, or

b) a cover provided with an adhesive that, if desired, contains penetration-enhancing agents,
from one to three matrix layer(s) which are each attached by means of a cover to the adhesive, leaving a border of adhesive uncovered, and which contain(s) the ester(s) of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one, optionally the oestrogen(s) and penetration-enhancing agents,
and a removable protective layer, or

c) an impermeable cover layer,
from one to three medicament reservoir(s) which is(are) located on or in the cover layer, which contain(s) the

ester(s) of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one, optionally the oestrogen(s) and, if desired, penetration-enhancing agents, from one to three polymer layer(s) that is(are) permeable to those components,
a permeable skin-adhesive layer optionally containing penetration-enhancing agents,
and a removable protective layer.

A transdermal therapeutic system according to Variant a) is a single matrix system. It may, for example, be of a round, oval or rectangular shape and may be produced as follows:

A solution or suspension of up to 40 % by weight active ingredient or active ingredient mixture, from 0 to 40 % by weight of a penetration-enhancing agent, from 30 to 70 % by weight of a medically customary adhesive, made up to 100 % by weight with a suitable volatile solvent, is spread onto a planar impermeable cover layer. After drying, a second and, if desired, subsequently even a third layer optionally containing active ingredient, penetration-enhancing agents and adhesive may be applied to that layer and dried. The matrix system is then provided with a removable protective layer.

If a medically customary matrix former that, after drying of the system, does not adhere or adheres only inadequately to the skin is used, then the system may additionally be covered or surrounded by a skin-adhesive before the removable protective layer is applied.

Suitable solvents and penetration-enhancing agents are, for example, the liquids of that kind already mentioned. Suitable medically customary adhesives are, for example, polyacrylates, silicones, polyurethanes, block polymers,

styrene/butadiene copolymers and natural or synthetic caoutchoucs, such as, for example, polyisobutylenes. Other suitable matrix formers are cellulose ethers, polyvinyl compounds or silicates. To increase the adhesiveness, the customary additives, such as, for example, tackifying resins and oils, may be added to the resulting matrix. It is furthermore possible to use crystallisation inhibitors, such as, for example, Kollidon® VA 64, in order to increase the physical stability of the system, as is described, for example, in WO 93/08797.

Suitable protective layers are all foils customarily used in transdermal therapeutic systems. Such foils are, for example, siliconised or fluoropolymer-coated.

As cover layer in this system there may be used, for example, 10 to 100 µm thick foils of polyethylene or polyester which may, if desired, be pigmented or metallised. The medicament layer applied thereto preferably has a thickness of from 20 to 500 µm. The delivery of the active ingredients preferably takes place over a surface area of from 5 to 100 cm^2.

In multi-layer matrix systems, the ester or esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one and, where applicable, the penetration-enhancers can be introduced, for example, into the matrix applied to the impermeable cover layer, while the layer or layers located underneath contain(s) the oestrogens and, where applicable, likewise penetration-enhancers. On the other hand, it is also possible to arrange a plurality of active-ingredient-containing matrices side by side in such a transdermal system.

A transdermal therapeutic matrix system according to

Variant b) may, for example, similarly be round, oval or rectangular and may be produced as follows:

A cover is coated with a skin-adhesive. There is then glued to the cover, per TTS, from one to three stamped-out areas of a matrix layer provided with an impermeable cover and containing the ester(s) of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one, optionally the oestrogen(s) and penetration-enhancing agents, in such a manner that the cover has a sufficient border for attachment to the skin and, in the case of a plurality of areas, also sufficient space between those areas, and the matrix layer is provided with a removable protective layer. The materials used in these matrix systems may be the same as in those of Variant a).

A transdermal therapeutic reservoir system according to Variant c) may, for example, similarly be round, oval or rectangular and may be produced as follows:

An impermeable foil is so deformed by means of heat and/or tension that from one to three depression(s) of from 0.1 to 3 ml capacity is(are) formed. The depression is filled with an active-ingredient-containing solution or suspension containing from 1 to 50 % by weight active ingredient or active ingredient mixture together with a penetration-enhancing agent. The active-ingredient-containing solution or suspension may also have been thickened with up to 10 % by weight matrix formers.

The covering of the reservoir towards the skin is provided by a welded-on or glued-on permeable polymer layer to which a permeable skin-adhesive layer and a removable protective layer are applied.

The above-mentioned penetration-enhancing agents may be used in that system. As the permeable polymer layer there is used, for example, a from 20 to 200 µm thick foil of cellulose esters, cellulose ethers, silicones or polyolefin compounds. By varying that polymer layer it is possible for the rate of diffusion of the active ingredient or active ingredient mixture to be varied within wide limits.

Suitable adhesives and protective layers are the same materials as those described for the transdermal therapeutic system according to Variant a).

When producing transdermal therapeutic systems having two or three active-ingredient-containing matrix layers or medicament reservoirs arranged side by side, it is often advantageous to incorporate the ester(s) of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one in the one matrix layer or medicament reservoir, and the oestrogen(s) in the other matrix layer or medicament reservoir. In such cases, the active-ingredient-containing matrix systems or medicament reservoirs may not only contain differing active ingredients but may also contain, in addition, differing penetration-enhancing agents.

In the case of the matrix systems according to Variant a) or b), sufficient spacing of the areas must be ensured in order to prevent diffusion of the active ingredients into the respective other area. In the case of the reservoir systems according to Variant c), it is possible to provide the individual reservoirs with polymer layers of differing permeability in order thereby to adapt the diffusion flow of the individual active ingredients to the particular requirements.

Further features of the transdermal systems according to the invention will be explained with reference to the accompanying drawings, which are not drawn to scale.

Fig. 1 shows a cross-section of a single, round matrix system according to Variant a), without the removable protective layer. It consists of the impermeable cover layer 1 and the medicament-containing matrix layer 2.

Fig. 2 shows a cross-section of a matrix system according to Variant b), without the removable protective layer. Fig. 3 is a plan view of that system. The system consists of the cover 3 that is provided with an adhesive layer 4. Attached to that adhesive layer by means of impermeable covers 5 and 7 are two medicament-containing matrix layers 6 and 8.

Fig. 4 shows a cross-section of a round, single-chamber reservoir system according to Variant c), without the removable protective layer. It consists of the impermeable cover layer 9, the medicament reservoir 10, the permeable polymer layer 11 and the skin-adhesive layer 12.

Fig. 5 shows a cross-section of a round, two-chamber reservoir system according to Variant c), without the removable protective layer. It consists of the impermeable cover layer 13, the two semi-circular medicament reservoirs 14 and 15, the permeable polymer layer 16 and the skin-adhesive layer 17.

Apart from transdermal therapeutic systems, other galenical preparations are also suitable for the transdermal administration of the esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one.

An emulsion gel for transdermal administration consists, for example, of the active ingredient or active ingredient mixture, penetration-enhancing agents, emulsifiers (it being possible for ambiphilic representatives of the penetration-enhancing agents to serve as emulsifiers) and, where applicable, matrix formers. A typical recipe consists of from 0.1 to 25 % by weight active ingredient or active ingredient mixture, from 0 to 10 % by weight emulsifier, from 0 to 5 % by weight matrix former, from 0 to 50 % by weight penetration-enhancing agents, and water to make up to 100 % by weight. The agent is emulsified in customary manner and, if necessary, customary antioxidants, preservatives, etc. are added thereto.

One-phase gels are obtained, for example, by dissolving or suspending the active ingredient or active ingredient mixture in solvents, such as water, lower alcohols or mixtures thereof, optionally with the addition of penetration-enhancing agents and thickening with matrix formers.

Typical recipes for such gels contain from 0.01 to 25 % by weight active ingredient or active ingredient mixture, from 1 to 20 % by weight matrix formers, and from 0 to 40 % by weight penetration-enhancing agents, made up to 100 % by weight with the solvent.

Those gels also may, if desired, contain antioxidants, preservatives, etc..

A typical spray recipe is, for example, as follows:

From 1 to 25 % by weight active ingredient or active ingredient mixture, from 0 to 20 % by weight matrix

formers, and from 0 to 60 % by weight penetration-enhancing agents, made up to 100 % with solvents and, where applicable, propellants. If compressed gas packs are used, the propellant may be omitted.

The agents according to the invention for transdermal administration which contain esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one may be used for the treatment of the same diseases as are the prior-known, for example orally administered, agents that contain highly active gestagens. In addition, the optionally oestrogen-containing preparations according to the invention may also be used for contraception. The agents according to the invention have special advantages in the treatment of diseases that require long-term treatment with a relatively high dose of the active ingredients. In this case, the frequency of administration can be substantially reduced and a substantially more uniform blood plasma level can be obtained. It is also advantageous that gastro-intestinal side-effects are not to be expected and, in the case of oestrogen-containing combination preparations, the first passage through the liver is avoided and the dose of oestrogen can be reduced.

Those advantages make the oestrogen-free monotherapeutic agents of the present invention appear especially suitable for treating, for example, endometriosis, gestagen-dependent tumours, benign breast diseases or premenstrual syndrome.

The transdermal administration of oestrogens in sequential or continuous combination with esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one offers special advantages, for example for the treatment of climacteric complaints, for the prevention

of osteoporosis, for regulation of the menstrual cycle and for stabilisation of the menstrual cycle.

The Working Examples that follow serve to illustrate the invention in greater detail. The following commercial products were used therein:

Polyester foil of 0.074 mm thickness (SkotchPak® 1009) manufactured by 3M; polypropylene foil (Celgard® 2500) manufactured by Celanese, liner foil Skotchpak® 1022 and 1360 manufactured by 3M; transfer adhesive 9871 manufactured by 3M, polyacrylic ester adhesive of the Sichello® J 6610-21 type manufactured by Henkel KG, polyisobutylene adhesive of the Oppanol® B 15SF type manufactured by BASF, polyacrylate ester adhesive of the Gelva® type manufactured by Monsanto, silicone adhesive of the X-7-4502 type manufactured by Dow Corning and hydroxypropylcellulose of the Klucel® HXF type manufactured by Hercules, and, as crystallisation inhibitors, Kollidon® 12 PF and Kollidon® VA64 manufactured by BASF.

A: Agents for transdermal administration

Example 1

0.8 g of 13-ethyl-17ß-hexanoyloxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one and 8.0 g of dimethyl isosorbide are introduced in succession, with stirring, into 62.4 g of a 50 % solution of silicone adhesive in benzine. After degassing the batch, the mixture is applied to polyester foil by means of a coating apparatus in such a manner that, after removal of the volatile solvent, a uniform film of 40 g/m^2 of solid coating is formed. This is then covered with a fluoropolymer-coated polyester liner. The laminate so obtained is divided into round individual plasters of 10 cm^2 surface area

using a stamping device and packed in aluminium foil. Fig. 1 shows a cross-section of that plaster, without the polyester liner. After removal of the liner foil the plaster adheres to the skin.

Analysis of the contents shows a uniform distribution of active ingredient averaging 0.08 mg/cm^2.

Example 2

10 g of 13-ethyl-17ß-hexanoyloxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one are introduced, with stirring, into 80 g of a 50 % solution of polyacrylic acid ester in ethyl acetate (g:g) and worked up as described in Example 1.

Analysis of the contents shows a uniform distribution of active ingredient averaging 8 mg/cm^2.

Example 3

5.0 g of 17ß-acetoxy-13-ethyl-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one and 10.0 g of isopropyl myristate are dissolved in succession, with stirring, in 170 g of a 50 % solution of polyisobutylene adhesive in acetone/benzine. After degassing the batch, the solution is applied to polyester foil using a coating device in such a manner that, after removal of the volatile solvent, a uniform film of 100 g/m^2 of solid coating is formed. This is then covered with a siliconised active-ingredient-free liner foil. The laminate so obtained is divided into individual plasters of 10 cm^2 surface area using a stamping device and packed in aluminium foil. After removal of the liner foil the plaster adheres to the skin.

The content of 17ß-acetoxy-13-ethyl-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one is, on average, 0.5 mg/cm^2.

Example 4

3.5 g of oestradiol, 3.5 g of 13-ethyl-17ß-hexanoyloxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one and 7.0 g of isopropyl myristate are in succession dissolved or suspended, with stirring, in 112 g of a 50 % solution of polyacrylic ester adhesive in acetone/benzine. After degassing the batch, the mixture is applied to polyester foil using a coating device in such a manner that, after removal of the volatile solvents, a uniform film of 70 g/m^2 of solid coating is formed. This is then covered with a siliconised active-ingredient-free liner foil. The laminate so obtained is divided into individual plasters of 5 cm^2 surface area using a stamping device and packed in aluminium foil. After removal of the liner foil the plaster adheres to the skin.

The content of oestradiol and ester of 13-ethyl-17ß-hexanoyloxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one is likewise 0.35 mg/cm^2 each.

Example 5

Two different segmented matrix systems having the shape shown in Figs. 2 and 3 are produced analogously to Example 1. Matrix system I consists of the matrix layer 8 provided with a polyester foil 7 and having the following composition: 1.0 mg of 17ß-acetoxy-13-ethyl-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one, 5.0 mg of isopropyl myristate, 34 mg of acrylate adhesive solid and 10 mg of Kollidon® VA64, and has a surface area of 5 cm^2.

Matrix system II consists of the matrix layer 6 provided with a polyester foil 5 and having the following composition: 2.0 mg of oestradiol, 10.0 mg of isopropyl myristate, 68 mg of acrylate adhesive solids and 20 mg of Kollidon® VA64, and has a surface area of 10 cm^2.

Both matrix systems are affixed to a covering foil coated with skin-adhesive, as shown in Fig. 3. After lining and stamping-out, plasters of the kind shown in Figs. 2 and 3 are thus obtained.

Example 6

A polyester foil of 7.4 cm diameter is so deformed by means of tension and heat that a round depression having a surface area of 10 cm^2 is formed. The depression is filled with 1 ml of a solution of 2.5 mg of ethynyloestradiol and 2.5 mg of 17β-butyryloxy-13-ethyl-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one in dimethyl isosorbide. A polypropylene or cellulose acetate butyrate foil is welded on at the edge. Depending upon the pressure per unit of time, the sealing temperature is between 70°C and 100°C. Adhesive film is transferred onto the permeable polymer layer. The plaster is provided with a liner and packed in aluminium foil.

Fig. 4 shows a cross-section of a plaster of that kind, without liner.

Example 7

Analogously to Example 6, a polyester foil is so deformed that two semi-circular depressions separated from each other by a strip and each having a surface area of

7.5 cm^2 are formed.

Reservoir I is filled with 0.75 ml of a suspension of 1.5 mg of 17ß-acetoxy-13-ethyl-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one in 1,2-propanediol and Reservoir II is filled with 0.75 ml of a suspension of 3.0 mg of oestradiol in 1,2-propanediol. Further production of the plaster is effected as described in Example 5.

Fig. 5 shows a cross-section of such a plaster, without liner.

Example 8

0.2 g of oestradiol, 0.02 g of 17ß-butyryloxy-13-ethyl-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one, 10.0 g of 1,2-propanediol and 10.0 g of isopropyl myristate are dissolved in succession in 76.78 g of ethanol (96 % by volume) or isopropanol. 3 g of hydroxypropylcellulose are then added to the solution and the air is removed from it. After a swelling time of 2 hours, the gel is introduced into aluminium tubes with a triple internal protective coating.

Analysis of the contents shows a homogeneous distribution of active ingredient in the gel, with values of from 95 % to 105 % of the desired value.

Example 9

20.00 g of 13-ethyl-17ß-hexanoyloxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one are dissolved in 1000 g of isopropyl myristate, and the solution is sterile-filtered and introduced under aseptic conditions into medicine bottles of 5 ml capacity.

B: Syntheses:

Example 1

5 g of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one are suspended in 34.5 ml (150 mmol) of hexanoic anhydride, 1.04 g of N,N-dimethyl-aminopyridine are added thereto and the mixture is stirred for one hour at 0°C and for a further 18 hours at 20°C. The mixture is then cooled to 0°C again and 2.0 g of potassium carbonate and 12.5 ml of methanol are added thereto, stirring is carried out for 3 hours and 10 ml of water are added. The mixture is extracted with ethyl acetate, and the ethyl acetate extract is washed, dried over sodium sulphate and concentrated in vacuo. The residue is chromatographed over a silica gel column using hexane/ethyl acetate 100:0 to 80:20, yielding 5.85 g of 13-ethyl-17ß-hexanoyloxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one having a melting point of 123-124°C.

Example 2

Under the conditions of Example 1, but using acetic anhydride, 17ß-acetyl-13-ethyl-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one having a melting point of 170-171°C is prepared.

Example 3

Under the conditions of Example 1, but using butyric anhydride, 17ß-butyryloxy-13-ethyl-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one having a melting point of 118-119°C is prepared.

~~Patent Claims~~

CLAIMS

1. Agent for transdermal administration, characterised in that it contains from one to three esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one having from 1 to 20 carbon atoms in the ester radical, optionally in combination with 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one and/or with from one to three oestrogen(s).

2. Agent for transdermal administration according to patent claim 1, characterised in that it contains esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one having from 2 to 12 carbon atoms in the ester radical.

3. Agent for transdermal administration according to patent claims 1 and 2, characterised in that it contains an ester of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one having from 2 to 8 carbon atoms in the alkanoyl radical.

4. Agent for transdermal administration according to patent claims 1 to 3, characterised in that there are used as oestrogen(s) oestradiol, oestriol, 17α-ethinyl-oestradiol, mestranol, 14α,17α-ethanooestra-1,3,5,(10)-triene-3,17ß-diol, 14α,17α-ethanooestra-1,3,5(10)-triene-3,16α,17ß-triol, or esters of those compounds.

5. Agent for transdermal administration according to patent claims 1 to 4, characterised in that the agent is a transdermal therapeutic system (TTS).

6. Agent for transdermal administration according to patent claim 5, characterised in that the transdermal therapeutic system consists of

a) an impermeable cover layer,
from one to three matrix layer(s) which adhere(s) to the cover layer, which contain(s) the ester(s) of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one, optionally the oestrogen(s) and, if desired, penetration-enhancing agents and is(are) permeable to those components, and which is(are) self-adhesive or covered or surrounded by a skin-adhesive that, if desired, contains penetration-enhancing agents,
and a removable protective layer, or

b) a cover provided with an adhesive that, if desired, contains penetration-enhancing agents,
from one to three matrix layer(s) which are each attached by means of an impermable cover to the adhesive, leaving a border of adhesive uncovered, and which contain(s) the ester(s) of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one, optionally the oestrogen(s) and penetration-enhancing agents,
and a removable protective layer, or

c) an impermeable cover layer,
from one to three medicament reservoir(s) which is(are) located on or in the cover layer, which contain(s) the ester(s) of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one, optionally the oestrogen(s) and, if desired, penetration-enhancing agents,
from one to three polymer layer(s) that is(are) permeable to those components,
a permeable skin-adhesive layer optionally containing penetration-enhancing agents,
and a removable protective layer.

7. Agent for transdermal administration according to patent claim 6, characterised in that it contains one

active-ingredient-containing matrix layer or one medicament reservoir.

8. Agent for transdermal administration according to patent claim 6, characterised in that it contains two or three active-ingredient-containing matrix layers or medicament reservoirs.

9. Agent for transdermal administration according to patent claim 8, characterised in that the active-ingredient-containing matrix layers or the medicament reservoirs contain different active ingredients.

10. The use of esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one having from 1 to 20 carbon atoms in the ester radical, optionally in combination with one or more oestrogen(s), for the preparation of an agent for the transdermal administration of the active ingredient or active ingredient mixture.

11. The use of esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one having from 1 to 20 carbon atoms in the ester radical, in combination with one or more oestrogen(s), for the preparation of an agent according to patent claim 10, characterised in that there are used as oestrogen(s) oestradiol, oestriol, 17α-ethynyloestradiol, mestranol, 14α,17α-ethanooestra-1,3,5(10)-triene-3,17ß-diol, 14α,17α-ethanooestra-1,3,5(10)-triene-3,16α,17ß-triol, or esters of those compounds.

12. The use of esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one having from 1 to 20 carbon atoms in the ester radical, optionally in combination with one or more oestrogen(s), for the

preparation of an agent according to patent claims 11 and 12, characterised in that the agent is a transdermal therapeutic system (TTS).

13. The use of esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one having from 1 to 20 carbon atoms in the ester radical, optionally in combination with one or more oestrogen(s), for the preparation of an agent according to patent claim 12, characterised in that it is a transdermal therapeutic system according to patent claims 6 to 9.

14. The use of oestrogen-free agents for transdermal administration according to patent claims 1 to 9 for transdermal contraception, for the treatment of endometriosis, for the treatment of gestagen-dependent tumours and for the treatment of premenstrual syndrome.

15. The use of agents for transdermal administration according to patent claims 1 to 9, optionally in combination with oestrogen-containing agents, for the treatment of climacteric complaints, for the prevention of osteoporosis, for regulation of the menstrual cycle, for stabilisation of the menstrual cycle and for transdermal contraception.

16. Esters of 13-ethyl-17ß-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one having from 2 to 8 carbon atoms in the alkanoyl radical.

17. 17ß-Acetoxy-13-ethyl-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one.

18. 17ß-Butyryloxy-13-ethyl-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one.

19. 13-Ethyl-17ß-hexanoyloxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one.

20. An agent for transdermal adminstration as claimed in claim 1, substantially as herein described and illustrated.

21. Use as claimed in any one of claims 10-13, substantially as herein described and illustrated.

22. Use as claimed in claim 14 or claim 15, substantially as herein described and illustrated.

23. A compound as claimed in claim 16, substantially as herein described and illustrated.

24. A new compound, new use of an ester as defined in claim 16, new use of oestrogen-free agents, or substance or composition for a new use in a method of treatment, substantially as herein described.

DATED THIS 17TH DAY OF JULY 1996

ADAMS & ADAMS
APPLICANTS PATENT ATTORNEYS

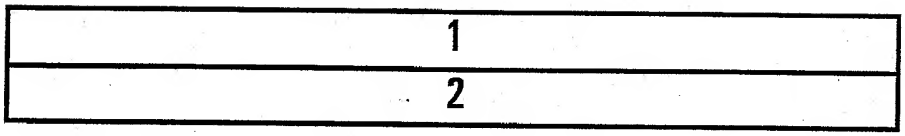


FIG 1

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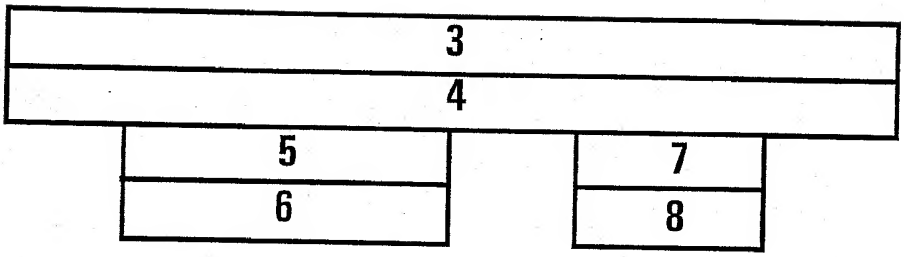

FIG 2

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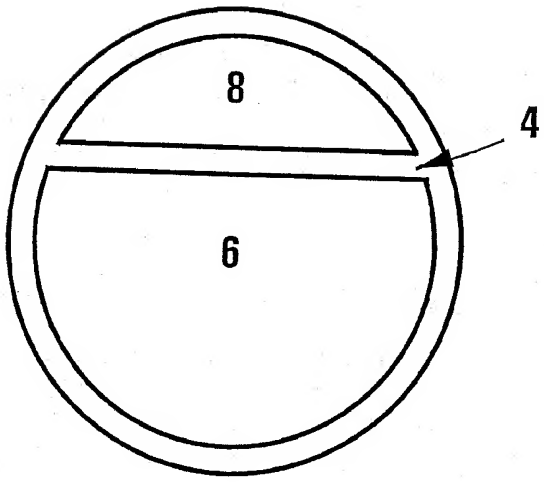

FIG 3

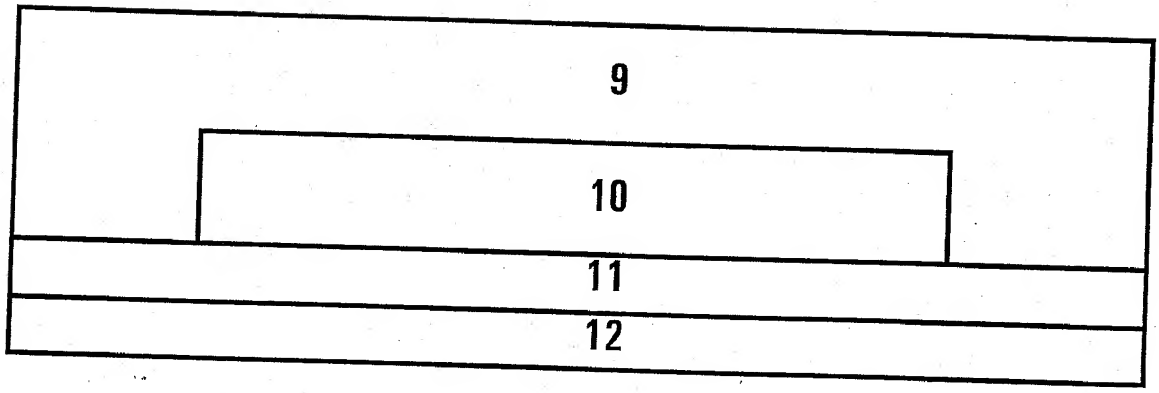

FIG 4

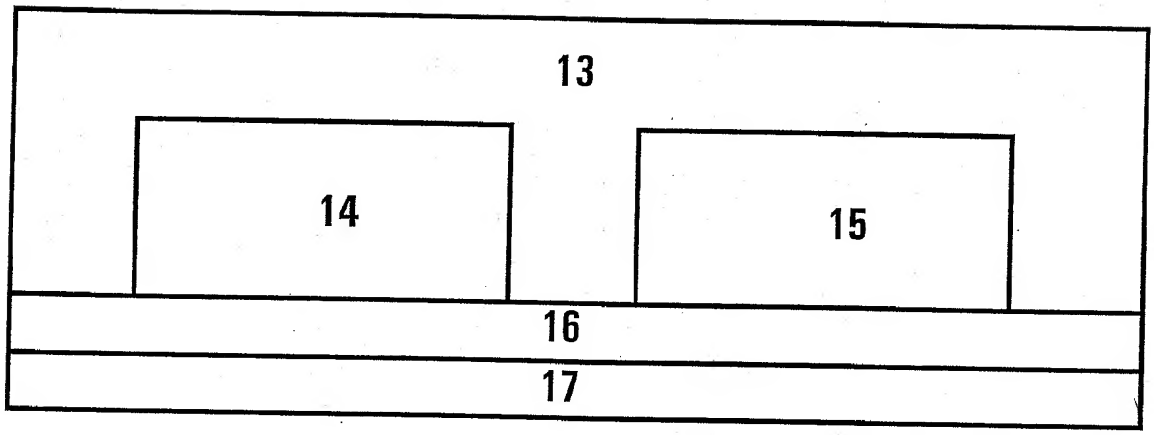

FIG 5